American Journal of Hematology 56:288–293 (1997)

Multiple Myeloma Associated With Diffuse Osteosclerotic Bone Lesions: A Clinical Entity Distinct From Osteosclerotic Myeloma (POEMS Syndrome)

Martha Q. Lacy,[1]* Morie A. Gertz,[1] Curtis A. Hanson,[2] David J. Inwards,[1] and Robert A. Kyle[1]

[1]Division of Hematology and Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota
[2]Division of Hematopathology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota

Multiple myeloma usually is characterized by the development of lytic bone lesions. Osteosclerotic myeloma is a rare entity characterized by a single or multiple osteosclerotic bone lesions and often accompanied by a demyelinating polyneuropathy. Multiple myeloma associated with widespread osteosclerotic lesions seen on radiographic studies is exceedingly rare. We describe 3 such cases and review 12 other cases described in the literature. Overall, the patients described herein had a clinical course that resembled multiple myeloma more than osteosclerotic myeloma. However, some patients had features of both diseases. Although rare, multiple myeloma should be included in the differential diagnosis of widespread osteosclerotic bone lesions. Am. J. Hematol. 56:288–293, 1997. © 1997 Wiley-Liss, Inc.

Key words: case history; differential diagnosis; gammopathy; monoclonal protein

INTRODUCTION

Development of lytic bone lesions is a major clinical feature that distinguishes monoclonal gammopathy of undetermined significance from multiple myeloma. Typically, the lesions are discrete and purely lytic. Osteosclerotic myeloma is a rare but well-defined entity characterized by a demyelinating polyneuropathy associated with a single or multiple sclerotic bone lesions. The bone lesions are often modest in size and usually involve the axial skeleton [1]. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) is associated with osteosclerotic bone lesions in a majority of cases [2]. Recent authors find the differentiation of POEMS syndrome from osteosclerotic myeloma to have no clinical value, but rather consider these two entities part of the clinical spectrum of plasma cell dyscrasias with polyneuropathy [2]. Bone marrow biopsy specimens generally contain <5% plasma cells and are associated with a small monoclonal protein, which is usually an IgA or IgG λ. Malignant plasma cells are detected in biopsy specimens from the sclerotic lesions [1]. Osteosclerotic myeloma differs from classical multiple myeloma, which typically presents with lytic bone lesions, >10% plasma cells in the bone marrow, and a large monoclonal protein in the serum or urine (or both). Multiple myeloma associated with widespread osteosclerotic lesions seen on radiographic studies is exceedingly rare. We describe three such cases and review the relevant literature.

REPORT OF CASES

Case 1

In February 1985, a 60-year-old woman had a monoclonal gammopathy of undetermined significance (MGUS), with an IgG κ monoclonal spike of 2.0 g/dL. In April 1987, she presented with a flu-like illness. She had no bone pain or other symptoms of myeloma. The physical examination findings were normal. On laboratory evaluation, she had a monoclonal spike of 3.11 g/dL. A 24-h urine collection contained 83 mg of protein, most of which was monoclonal κ. Other laboratory findings in-

Contract grant sponsor: National Cancer Institute; Contract grant number: CA62242.

*Correspondence to: Martha Q. Lacy, M.D., Mayo Clinic, 200 First Street SW, Rochester, MN 55905.

Received for publication 29 June 1996; Accepted 9 July 1997

cluded the following: hemoglobin, 12.1 g/dL; leukocytes, 6.9×10^9/L; platelets, 166×10^9/L; and the serum levels of calcium and creatinine, 8.8 mg/dL and 1.0 mg/dL, respectively. Alkaline phosphatase was increased at 333 U/L (normal, 84 to 218 U/L) and was skeletal in origin. A bone marrow biopsy specimen contained 80% plasma cells, with a plasma cell labeling index (PCLI) of 0.4% (normal, <0.8%) [3]. A metastatic bone survey showed diffuse sclerosis involving the spine, pelvis, and proximal femurs and humeri (Fig. 1).

The patient was observed without therapy for myeloma until September 1992, when the hemoglobin value was 8.9 g/dL and monoclonal protein was 5.51 g/dL. A bone survey again showed diffuse osteosclerosis but with new lytic lesions in the skull. The initial treatment was with erythropoietin, but there was no response to treatment. Beginning in April 1993, the patient received treatment with melphalan and prednisone. The patient had no response to the chemotherapy and had progressive cytopenias. Treatment with melphalan and prednisone was discontinued after 1 year. She was observed without treatment from April 1994 to April 1995, at which time she had pneumococcal pneumonia and a rising monoclonal spike to 7.0 g/dL. Chemotherapy with vincristine, doxorubicin, and dexamethasone was instituted, and she had a response. At latest follow-up (November 1995), the monoclonal protein was 3.12 g/dL.

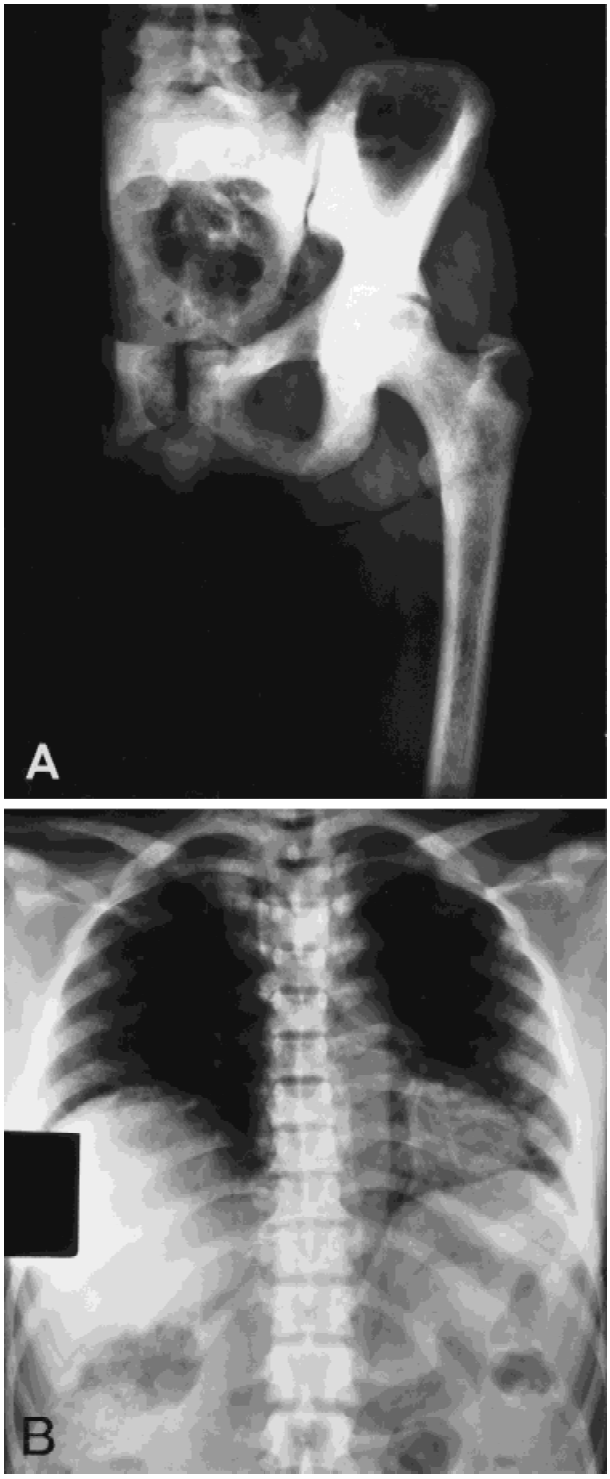

Fig. 1. Patient 1. A and B: Diffuse osteosclerosis seen on metastatic bone survey.

Case 2

A 53-year-old man presented in October 1992 with back pain of 1-month's duration. Radiography revealed innumerable small osteosclerotic lesions throughout the vertebral bodies, ribs, pelvis, and proximal femurs and humeri (Fig. 2). Hemoglobin was 16.3 g/dL; leukocytes, 4.5×10^9/L; platelets, 201×10^9/L; and the serum levels of calcium and creatinine, 10.2 mg/dL and 1.3 mg/dL, respectively. Serum protein electrophoresis, immunoelectrophoresis, and immunofixation failed to show a monoclonal protein. On 24-h urine collection, he excreted 150 mg of monoclonal κ light chains. Bone marrow biopsy revealed 20% plasma cells with a PCLI of 0.4%.

By January 1993, the patient's back pain had worsened. The results of a bone survey were unchanged, but a computed tomographic scan showed mixed lytic and sclerotic lesions involving L-5, the sacrum, and the iliac bones (Fig. 3). The urine monoclonal κ protein was 202 mg/24 hr. Chemotherapy was initiated with melphalan and prednisone. There was no objective evidence of disease progression, and he had no relief of his pain. After 6 months, the chemotherapy was changed to a high dose of cyclophosphamide. Excessive myelosuppression and febrile neutropenia developed, and the regimen was discontinued. In January 1994, he received monthly treatments with intravenously administered pamidronate. At latest follow-up (November 1995), he had a urine monoclonal protein of 140 mg/24 hr, no new bone lesions, and no pain.

Fig. 2. Patient 2. Innumerable small osteosclerotic bone lesions seen on metastatic bone survey.

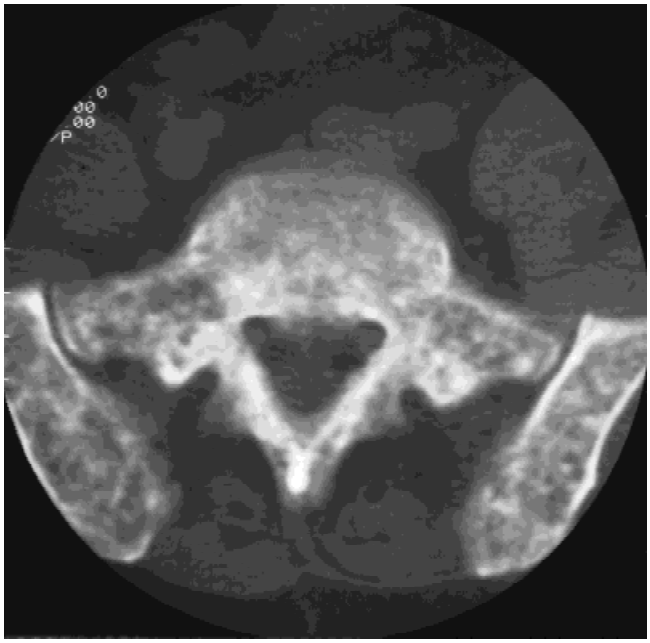

Fig. 3. Patient 2. Mixed lytic and sclerotic lesions seen on computed tomographic scan of vertebral body L-5.

Case 3

A 59-year-old woman presented in February 1994 with dyspnea on exertion. Laboratory findings included the following: hemoglobin, 6.0 g/dL, leukocytes, 4.5 × 10^9/L; platelets, 137 × 10^9/L; and serum levels of calcium and creatinine, 9.3 mg/dL and 1.1 mg/dL, respectively. Alkaline phosphatase was 369 U/L and was skeletal in origin. A bone marrow biopsy specimen showed that the marrow was replaced completely with plasma cells. The physical examination findings were normal. She had a 4.08 g/dL IgA λ spike in the serum. Urine studies showed 234 mg/24 hr of protein excretion, with 66% monoclonal λ with an IgA λ fragment. The peripheral blood labeling index showed the presence of circulating plasma cells. The results of a technetium bone scan were normal. A metastatic bone survey showed diffuse osteosclerosis in the vertebral bodies, ribs, pelvis, and proximal femurs and humeri (Fig. 4).

She received treatment with melphalan and prednisone. After 15 months of chemotherapy, the monoclonal protein had decreased to 2.4 g/dL, and she had been transfusion-independent for 15 months. In September 1995, she again began to require transfusions. By March 1996, the IgA level had increased to 5,410 mg/dL.

DISCUSSION

Osteosclerotic myeloma is a rare but well-defined entity. It differs from multiple myeloma in that the patients are younger and the disease course is more indolent. The patients usually present with neuropathy and rarely have bone pain. Bone marrow biopsy specimens generally contain <5% plasma cells. Erythrocytosis and thrombocytosis are common. Hypercalcemia and renal insufficiency are rare in patients with osteosclerotic myeloma. When osteosclerotic myeloma is associated with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein elevation, and skin changes, it is known as POEMS syndrome [1]. The major difference between patients with osteosclerotic myeloma and the ones we describe is the extent of bone disease seen on radiographic imaging. Most patients with osteosclerotic myeloma have one or a few small isolated sclerotic bone lesions. The largest series of POEMS patients is a group of 109 patients from Japan. Bone radiographic findings were described in 84 patients and lesions were found in 61. They included scattered osteosclerotic spots, mixed sclerotic and lytic changes, tumor formation with sclerotic septa, periosteal calcium deposition, and a few purely lytic lesions [4]. None had diffuse osteosclerotic bone lesions that involved virtually all the axial skeleton, as seen in our patients.

Myeloma associated with widespread osteosclerosis seen on radiologic examinations was first described by Sharnoff et al. in 1954 [5]. In addition to this first report, we have identified 11 other reports in the English-language literature [6–15]. The clinical features of the patients reported in the literature and those of our three patients are summarized in Table I.

Overall, the 12 patients described in the literature and the 3 we describe had a clinical course that resembled multiple myeloma more than osteosclerotic myeloma.

TABLE I. Comparison of Reports of Patients With Myeloma Associated With Widespread Osteosclerotic Lesions*

Author	Age, yr/sex	Serum M-protein (g/dL)	Urine monoclonal protein (g/24 hr)	Hgb (g/dL)	No. of platelets $\times 10^9$/L	Calcium (mg/dL)	Creatinine (mg/dL)	Physical exam findings	Bone/marrow pathology	Radiologic findings	Survival	Clinical presentation
Sharnoff et al., 1954 [5]	68/M	8.0							Atypical PC	Diffuse osteosclerosis		
Videbæk, 1956 [6]	68/F	5.4						Splenomegaly	Myelofibrosis/ myelosclerosis	Diffuse osteosclerosis	16 months	Anemia
Engels et al., 1960 [7]	40/M	9.5							Thickened trabeculae around groups of PC	Innumerable osteosclerotic lesions		Subcutaneous plasmacytomas
	65/M	Not given							Sternal aspirate with 35% PC	Diffuse osteosclerosis		Anorexia, RUQ pain
Fairley et al., 1964 [8]	61/F	1.97	Bence Jones	3.8	30			Splenomegaly	Myelofibrosis, myelosclerosis marrow PC infiltration	Diffuse osteosclerosis; later developed lytic lesions	20 mo	Anemia
Clarisse and Staple, 1971 [9]	68/F	κ		10.1	Normal				Increased PC	Diffuse osteosclerosis		Anemia
Heitzman and Markarian, 1973 [10]	80/F	IgA		8.7	30		0.9	Hepatomegaly	Sheets of PC, sclerotic trabeculae	Diffuse osteosclerosis		Anemia
Brown and Paterson, 1973 [11]	65/F	2.92/IgA κ	Free κ	8.6		11.5			Formation of new bone around pockets of PC	Diffuse osteosclerosis; femoral lytic lesions		Hip pain
Himmelfarb et al., 1974 [12]	74/M	7.0/IgA						Hepatomegaly	Thickened bony trabeculae adjacent to groups of PC	Diffuse osteosclerosis	11 months	Back pain, anemia
MacCallum et al., 1988 [13]	40/M	3.1/IgD λ	19.8/free λ	7.7	130	2.4 mmol/L	791 μmol/L	Splenomegaly, adenopathy	Infiltrated with PC, increased trabeculae, increased reticulin	Diffuse osteosclerosis	14 months	Anemia and bone pain
McCluggage et al., 1995 [14]	51/F	4.6/IgA λ	4.6/IgA λ	8.0	165	2.49 mmol/L	Normal		Thickened bony trabeculae, grade 4 collagen fibrosis, clumps of PC	Diffuse osteosclerosis, later developed lytic lesions	60 months	Anemia and back pain
Kuo and Shih, 1995 [15]	71/M	2.1/IgG λ		4.1	61	7.8	1.2		Thickened bony trabeculae, packed with PC	Diffuse osteosclerosis	22+ months	Anemia and weight loss
This study, patient 1	60/F	3.11/IgG κ	0.083/IgG κ	12.1	166	8.8	1.0		Sheets of PC; Sclerotic bone formation; new bone formation with focal paratrabecular myelofibrosis	Diffuse osteosclerosis, later developed lytic lesions	10 years	Initially asymptomatic, anemia when treatment instituted
This study, patient 2	53/M	None	0.15/free κ	16.3	201	10.2	1.3		Small foci of atypical PC that are not directly associated with fibrosis; sclerotic bone formation; focal paratrabecular myelofibrosis	Innumerable osteosclerotic lesions; later developed mixed lytic/sclerotic lesions	37+ months	Severe back pain
This study, patient 3	59/F	4.08/IgA λ	0.234/IgA λ	6.0	137	9.3	1.1		Sclerotic bone formation; sheets of PC; no fibrosis	Diffuse osteosclerosis	18+ months	Anemia

*PC, plasma cells; RUQ, right upper quadrant.

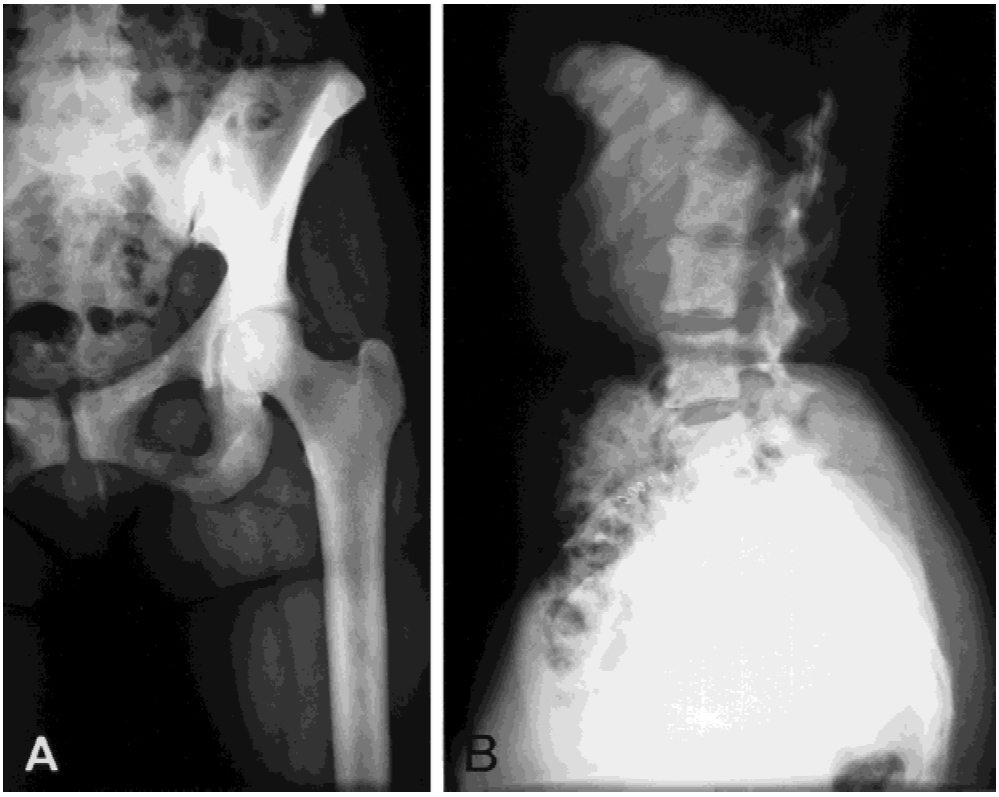

Fig. 4. Patient 3. A and B: Diffuse osteosclerosis seen on metastatic bone survey.

All the patients had osteosclerotic lesions that were more extensive than those of osteosclerotic myeloma. Presenting symptoms consisted of bone pain in 5 patients and symptoms of anemia in 10, symptoms that rarely are seen in conjunction with osteosclerotic myeloma. Patients with osteosclerotic myeloma frequently present with symptoms of peripheral neuropathy. None of our patients had evidence of neuropathy. Several patients initially presented with diffuse osteosclerosis but subsequently had lytic lesions. Lytic lesions are unusual with osteosclerotic myeloma. None of the patients we reviewed had the laboratory abnormalities that are found with osteosclerotic myeloma, such as thrombocytosis or erythrocytosis. The literature suggests that the monoclonal proteins associated with POEMS are almost exclusively IgA λ or IgG λ [2,4]. This was not seen in the patients we describe and further supports the observation that these patients have a clinical course more like multiple myeloma than like POEMS.

The median survival after diagnosis for patients with multiple myeloma is 36 months [16]. Only eight of the reports in the literature included information about long-term follow-up. Initial reports suggested a poor prognosis for this group of patients, with most patients dying less than 2 years after diagnosis. Two of our patients had a more indolent course than that described in the literature. McCluggage et al. [14] described a patient who survived for 5 years after diagnosis. Kuo and Shih [15] reported on a patient with plasma cell leukemia who achieved a complete remission and was still alive and in remission 22 months after the diagnosis. Whether these cases indicate a better prognosis for patients with this variant remains to be determined.

The pathogenesis of diffuse osteosclerosis in myeloma is not clear. It is known that the lytic lesions of myeloma likely are mediated through the stimulation of osteoclasts by several cytokines, including IL-1β and tumor necrosis factor [17]. Osteosclerotic lesions likely result from an uncoupling of osteoblast and osteoclast cell activities. Prostate cancer cells, a malignancy often associated with osteosclerotic bone lesions, synthesize platelet-derived growth factor and transforming growth factor β, cytokines known to stimulate osteoblasts [18]. Platelet-derived growth factors also are thought to be responsible for the diffuse fibrosis and osteosclerosis found in agnogenic myeloid metaplasia and other myeloproliferative diseases [19]. A similar mechanism possibly accounts for the sclerotic bone lesions in patients with myeloma.

ACKNOWLEDGMENTS

Funded in part by a grant from the National Cancer Institute (CA 62242).

REFERENCES

1. Kyle RA, Dyck PJ: Osteosclerotic myeloma (POEMS syndrome). In Dyck PJ, Thomas PK, Griffin JW, Low PA, Poduslo JF (eds): ''Peripheral Neuropathy,'' Vol. 2, 3rd ed. Philadelphia: WB Saunders Company, 1993, p 1288.
2. Miralles GD, O'Fallon JR, Talley NJ: Plasma-cell dyscrasia with polyneuropathy. The spectrum of POEMS syndrome. New Engl J Med 327:1919, 1992.
3. Greipp PR, Lust JA, O'Fallon WM, Katzmann JA, Witzig TE, Kyle RA: Plasma cell labeling index and beta 2-microglobulin predict survival independent of thymidine kinase and C-reactive protein in multiple myeloma. Blood 81:3382, 1993.
4. Takatsuki K, Sanada I: Plasma cell dyscrasia with polyneuropathy and endocrine disorder: Clinical and laboratory features of 109 reported cases. Jpn J Clin Oncol 13:543, 1983.
5. Sharnoff JG, Belsky H, Melton J: Plasma cell leukemia or multiple myeloma with osteosclerosis. Am J Med 17:582, 1954.
6. Videbæk A: Unusual cases of osteomyelosclerosis. Acta Med Scand 153:459, 1956.
7. Engels EP, Smith RC, Krantz S: Bone sclerosis in multiple myeloma. Radiology 75:242, 1960.
8. Fairley GH, Jackson DC, McDonald P: Osteosclerosis in myelomatosis. Br J Radiol 37:852, 1964.
9. Clarisse PD, Staple TW: Diffuse bone sclerosis in multiple myeloma. Radiology 99:327, 1971.
10. Heitzman ER, Markarian B: Diffuse bone sclerosis. N Y State J Med 73:764, 1973.
11. Brown TS, Paterson CR. Osteosclerosis in myeloma. J Bone Joint Surg Br 55:621, 1973.
12. Himmelfarb E, Sebes J, Rabinowitz J: Unusual roentgenographic presentatinos of multiple myeloma. Report of three cases. J Bone Joint Surg Am 56:1723, 1974.
13. MacCallum PK, Freemont AJ, Geary CG, Liu Yin JA: A case of IgD myeloma presenting as diffuse osteosclerosis. J Clin Pathol 41:486, 1988.
14. McCluggage WG, Jones FG, Hull D, Bharucha H: Sclerosing IgA multiple myeloma. Acta Haematol 94:98, 1995.
15. Kuo MC, Shih LY: Primary plasma cell leukemia with extensive dense osteosclerosis: Complete remission following combination chemotherapy. Ann Hematol 71:147, 1995.
16. Kyle RA: Multiple myeloma and other plasma cell disorders. In Hoffman R, Benz EJ Jr, Shattil SJ, Furie B, Cohen HJ, Silberstein LE (eds): ''Hematology: Basic Principles and Practice.'' New York: Churchill Livingstone, 1995, p 1354.
17. Bataille R, Chappard D, Klein B: Mechanisms of bone lesions in multiple myeloma. Hematol Oncol Clin North Am 6:285, 1992.
18. Koutsilieris M, Rabbani SA, Bennett HP, Goltzman D: Characteristics of prostate-derived growth factors for cells of the osteoblast phenotype. J Clin Invest 80:941, 1987.
19. Hoffman R, Silverstein MN: Agnogenic myeloid metaplasia. In Hoffman R, Benz EJ Jr, Shattil SJ, Furie B, Cohen HJ, Silberstein LE (eds): ''Hematology: Basic Principles and Practice.'' 2nd ed. New York: Churchill Livingstone, 1995, p 1160.